Probiotics: A Review

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ABSTRACT

- *Objective:* To review the current evidence on the health benefits and adverse effects of probiotics.
- *Methods:* Review of the literature.
- *Results:* The efficacy of probiotics is strain-dependent. There is good evidence to support probiotic use in the treatment of acute diarrheal diseases, prevention of antibiotic-associated diarrhea, and prevention of pouchitis. However, there is insufficient evidence to recommend probiotics for use in other clinical conditions. Most of the studies have been marked by clinical and methodological differences, pointing to the need for well-designed clinical trials to properly assess the efficacy of probiotics. The side effects of probiotics are generally mild, but serious infections have been reported, especially in the elderly, patients with intravenous catheters, and the immunocompromised.
- *Conclusion:* While probiotics are beneficial in few clinical conditions, there is a need for additional investigations to better define their proper use in clinical practice.

The human gastrointestinal tract is colonized with a diverse population of microbial flora that not only provide digestive function but also contribute to intestinal epithelial homeostasis and innate immunity. Alteration of the microflora has been implicated in the pathogenesis of various diseases, including infectious, inflammatory, allergic, and immunologic conditions. Recognition of the importance of intestinal microflora has generated much interest in probiotic use to promote and maintain health. In this paper, we review the current evidence on the health benefits and adverse effects of probiotics.

OVERVIEW

Probiotics have been defined as live microorganisms that when administered in adequate amounts confer a health benefit on the host [1]. The use of probiotics goes back thousands of years, with intake of probiotics in the form of yogurt, cheese, and fermented foods as part of a regular diet. However, the health benefits of probiotics were first described a century ago by Russian Nobel laureate Elie Metchnikoff [2], who postulated that the longevity of Bulgarian peasants was due to the consumption of sour milk, which contains lactic acid bacteria whose growth in the intestine displaces disease-producing organisms.

Most commonly used probiotics come from the genera *Lactobacillus* and *Bifidobacterium*. Others include *Streptococcus thermophilus*, nonpathogenic strains of *E. coli, Enterococcus, Bacillus,* and yeasts such as *Saccharomyces boulardii.* In their research, Dunne et al used the following criteria for in vitro selection of probiotic bacteria: they should be of human origin, nonpathogenic, resistant to processing, resistant to gastric acid and bile, be able to attach to gut epithelial tissue, colonize the gastrointestinal tract, produce antimicrobial substances, modulate immune responses, and influence metabolic activities of the host [3]. Although human origin of microorganisms and colonization of the gastrointestinal tract were criteria, some strains have been isolated from other animals [4], and probiotics are now being investigated as topical agents and vaginal suppositories as well. Another important consideration is the need for a sufficient number of microbes to survive throughout the shelf life of the product.

MECHANISM OF ACTION

There are various proposed mechanisms that describe how different probiotics work, and they vary depending on the strain of probiotic used. The effects of probiotics also depend on the dosage and route of administration. Thus the mechanisms of action cannot be extrapolated to all the probiotics. Proposed mechanisms include:

- Compete against the pathogenic bacteria to bind to the intestinal epithelial cells [5].

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- Enhance intestinal epithelial barrier function by increasing the production of mucin [6], preventing injury of the epithelium from pathogens [7] and reducing cell permeability [8]. They may also enhance the mucosal barrier function by inducing expression of antimicrobial peptides like defensins [9].
- Inhibit the growth of the pathogens by secreting another class of antimicrobial peptides like bacteriocins [10] and reuterin [11]. Some of the probiotics, particularly lactic acid bacteria, inhibit the growth of the pathogens by creating an acidic environment through the production of organic acids [12].
- Enhance the production of serum IgA as well secretory IgA, which plays a crucial role in intestinal humoral immunity [13,14].
- Enhance phagocytosis [15], increase activity of natural killer cells [16], promote cell-mediated immunity [17] and stimulate various other nonspecific immune responses against pathogens.
- Down-regulate pro-inflammatory cytokine production [18], prevent apoptosis [19] and suppress T cell proliferation [20], thus preventing various inflammatory conditions.
- Produce hydrogen peroxide to suppress the pathogens associated with bacterial vaginosis [21].

In general, there is a wide range of immunomodulatory, anti-inflammatory and antimicrobial properties of probiotics that have been observed in vitro that are presumed to promote health and well being. However, as O'Hanlon et al noted, in vitro findings may not reflect in vivo effects; in the physiological environment, they found that lactic acid, not hydrogen peroxide, produced by lactobacilli helps to suppress bacteria associated with bacterial vaginosis [22].

HEALTH BENEFITS IN VARIOUS DISEASE CONDITIONS

Acute Diarrheal Disease

There is now growing evidence to support that probiotics are effective in both prevention and treatment of acute diarrhea in children and adults. A meta-analysis has shown that probiotics reduced mean duration of diarrhea by 13 hours, reduced treatment failure by 38%, and was also effective in preventing diarrhea in children [23]. A recent Cochrane review of 63 randomized and quasi-randomized controlled trials, 56 of which involved infants and children, concluded that probiotics were effective in reducing the mean duration of diarrhea by about 25 hours; the likelihood of diarrhea lasting ≥ 4 days was reduced by 59%; the stool frequency decreased by approximately 1 less bowel movement on day 2 after the probiotic use, and there were no adverse events noted [24]. The authors noted a significant variation in the effect size between the different studies and emphasized the need for more research on the use of various probiotic agents in specific groups of patients. A review of 10 randomized, double-blind, placebo-controlled trials by Szajewska et al reported the efficacy of probiotics in the treatment of acute infectious diarrhea particularly due to rotavirus gastroenteritis in infants and children and suggested that the most consistent result was seen with *Lactobacillus GG* [25]. Another meta-analysis of randomized controlled trials by Szajewska et al evaluated the effectiveness of *S. boulardii* and found that *S. boulardii* also reduces the duration of diarrhea in children [26].

Antibiotic-Associated Diarrhea and *Clostridium difficile*

Two meta-analyses concluded that probiotics, particularly *S. boulardii* and *Lactobacilli*, could be potentially used to prevent antibiotic-associated diarrhea in the general population [27,28]. A meta-analysis of randomized placebo-controlled trials in the pediatric group by Johnston et al showed a protective effect of probiotics to prevent antibiotic-associated diarrhea, but the finding was not statistically significant in the intention-to-treat analysis. A subgroup analysis further illustrated that higher daily dose ($5.5–40 \times 10^9$) showed significant effect but lower daily dose (2×10^9) was not statistically significant [29]. Another meta-analysis in children included 6 randomized placebo-controlled trials and demonstrated a reduction in the risk of antibiotic-associated diarrhea with probiotic use [30]. Further subgroup analysis suggested that the efficacy varied depending on the strain of probiotics used. It showed significant risk reduction of antibiotic-associated diarrhea with the use of *Lactobacillus* GG, *S. boulardii* and the combination of *B. lactis* and *Streptococcus thermophilus*, but there was no statistically significant difference with the use of the combination of *L. acidophilus* and *Bifidobacteruim* or *L. acidophilus* and *L. bulgaricus*. Szajewska et al specifically evaluated the effectiveness of *S. boulardii* in a meta-analysis of 5 randomized controlled trials and found that *S. boulardii*

is effective in the prevention of antibiotic-associated diarrhea in children and adults [31].

A Cochrane review of 4 small randomized studies [32] evaluated the efficacy of probiotics with or without vancomycin or metronidazole for the treatment of a first episode or recurrent *C. difficile* colitis in adults. A benefit was found in only 1 study, by McFarland et al [33], in which the patients received *S. boulardii*; they were less likely to develop recurrent *C. difficile* infection, but the benefit was not seen in the patients with an initial episode of *C. difficile* infection. The study by Surawicz et al [34] found that *S. boulardii* was effective in reducing the recurrence of *C. difficile* infection only when combined with high-dose vancomycin. There were no benefits seen in other studies included in the review and the authors concluded that there was insufficient evidence to support the use of probiotics alone or with antibiotic therapy for the treatment of *C. difficile* colitis [32]. In contrast, a meta-analysis by McFarland [35] reported that *S. boulardii*, *L. rhamnosus* GG, and mixtures of 2 probiotics were effective in the prevention of antibiotic-associated diarrhea. The main limitation of the meta-analysis was that among the various studies there was a lack of standardization when using a combination treatment regimen for the therapy of *C. difficile* colitis.

In summary, the meta-analyses support the use of probiotics in the treatment and prevention of antibiotic-associated diarrhea but the results are conflicting for its use in *C. difficile* infection. However, many providers advocate the use of probiotics in the prevention and treatment of *C. difficile* infection along with the standard therapy based on the anecdotal evidence.

Inflammatory Bowel Disease

It has been postulated that alteration of normal intestinal microflora plays an important role in the pathogenesis of inflammatory bowel disease. Hence, it seems intuitive that replenishing or modifying the microflora with probiotic administration may prevent or treat these conditions.

A Cochrane review of 4 randomized trials found no additional benefit from probiotic use in combination with standard therapy versus standard therapy alone for induction of remission in ulcerative colitis; however; there was some suggestion that probiotics may reduce the disease activity [36]. A systematic review by Zigra et al involving 9 randomized controlled studies failed to demonstrate a statistically significant difference in the efficacy of probiotics versus the control group for remission in ulcerative colitis [37]. A more recent meta-analysis by Sang et al showed beneficial effect of probiotics in maintaining remission but not in the induction of remission of ulcerative colitis. Further subgroup analysis demonstrated that there was a statistically significant difference in the rate of remission in the *Bifidobacterium* subgroup but not in the *E. coli* and VSL#3 *Lactobacillus* subgroups. Also, there was a statistically significant difference noted in the placebo trials but not in the nonplacebo trials [38].

Pouchitis is one of the complications in the patients with ulcerative colitis who undergo proctocolectomy with ileal pouch anal anastomosis. A meta-analysis of 5 randomized placebo-controlled trials established the benefit of probiotics in reducing the relapse of pouchitis [39]. Gionchetti et al also found that probiotic therapy with VSL#3 was effective in preventing the onset of acute pouchitis, thus opening the door for using probiotics as prophylaxis after ileal pouch anal anastomosis [40].

In Crohn's disease, meta-analyses to date [41,42] have failed to demonstrate the efficacy of probiotics for maintenance of remission and point to the need for larger trials to assess the benefit. In sharp contrast, a meta-analysis by Shen et al reported that *L. rhamnosus* administered as a maintenance therapy may instead increase the relapse rate in Crohn's disease [43].

Irritable Bowel Syndrome

The pathophysiology of irritable bowel syndrome (IBS) is not well known; however, alteration in the intestinal flora has been postulated as one of the etiologies. There is also no cure, so the treatment is mainly focused on symptom relief, and probiotics have been tried as a therapeutic modality. Several different meta-analyses assessed the use of probiotics in the treatment of IBS and they have shown promising results. A meta-analysis of 8 randomized, placebo-controlled trials by Nikfar et al suggested that probiotics may improve symptoms of IBS [44]. Similarly, McFarland, in a meta-analysis of 20 randomized controlled trials, also demonstrated that the use of probiotics was associated with improvement of global IBS symptoms as a primary outcome and less abdominal pain as a secondary outcome [45]. A systematic review of 10 randomized controlled trials by Moayyedi et al showed that probiotics were effective in the treatment of IBS. In the subgroup analysis, the study also showed that there was a statistically sig-

nificant improvement in pain scores and flatulence. Though improvement was also seen in bloating, it failed to reach statistical significance and there was no statistically significant change in urgency with probiotic use [46]. Another meta-analysis by Hoveyda et al of 14 randomized placebo-controlled trials suggested improvement in overall symptoms after administration of probiotics. The subgroup analysis demonstrated a statistically significant improvement in the abdominal pain, flatulence, and bloating using dichotomous data; however, improvement was not statistically significant when continuous data were used [47].

Traveler's Diarrhea

A meta-analysis of 12 randomized controlled trials by McFarland [48] found that on the whole, several probiotics were efficacious in the prevention of traveler's diarrhea. Of the 12 trials reviewed, 6 reported significant difference in the prevention of traveler's diarrhea in the probiotic treated group. Of the remaining 6 studies, one trended towards efficacy of probiotics and the remaining 5 demonstrated no difference between the probiotic-treated and control groups [48].

Helicobacter pylori Infection

A meta-analysis of 14 randomized trials suggested that probiotics supplementation increased the eradication rate and reduced the risk of side effects from the therapy for *H. pylori* [49]. In contrast, Szajewska et al, in a randomized, double-blind, placebo-controlled trial in children, found no significant difference with *Lactobacillus* GG supplementation in eradication rate or side effects [50]. Similarly, other studies have also found no significant difference in the eradication rate of *H. pylori* with probiotic supplementation [51,52].

Other Gastrointestinal Conditions

Probiotics have also been tried with some success in the prevention of uncomplicated diverticular disease [53] and diverticulitis [54], reduction of symptoms from collagenous colitis [55], treatment of functional constipation [56], prevention of necrotizing enterocolitis in preterm infants [57], and treatment of functional abdominal pain disorders in children [58]. Though different strains of probiotics have been effectively used in lactose intolerance, a systematic review by Levri et al found that probiotics did not reduce the signs and symptoms of lactose intolerance [59]. Capurso et al reviewed the current literature on the effects of probiotics in acute pancreatitis and found some benefit [60]. In contrast, the PROPATRIA study, a large double-blind placebo-controlled trial, showed that enterally administered probiotic prophylaxis did not reduce the risk of infectious complications in acute severe pancreatitis and was also associated with an increased mortality risk [61]. However, several criticisms of this study have been pointed out with regards to the choice of probiotics used, randomization, and increased bowel ischemia observed in the probiotic group [62]. There are also few promising results from studies supporting the use of probiotics alone or with prebiotics in the treatment of hepatic encephalopathy [63–65]. A case report of resolution of prolonged cryptosporiodiosis with probiotic treatment was intriguing [66]. In vitro and animal studies have suggested that probiotics may also have a role in prevention of colorectal cancer [67]. Probiotics may also have benefits in preventing radiation-[68] and chemotherapy-induced diarrhea [69]. In a review, Teughels et al concluded that probiotics may also have a role in promoting oral health and preventing periodontal diseases but also suggested the need for properly designed clinical studies [70].

Allergic Conditions

The literature on probiotics use in allergic conditions is controversial. Weston et al and Kalliomaki et al demonstrated that probiotics may be effective in reducing the severity of atopic dermatitis and prevent atopic disease in children at high risk, respectively [71,72]. In contrast, a randomized, double-blind, placebo-controlled trial by Kopp et al showed no effect on incidence or severity of atopic dermatitis in children with probiotics supplementation. Instead, the probiotic use was associated with increased episodes of wheezing bronchitis [73]. A systematic review of randomized controlled trials by Vliagoftis et al suggested that probiotics may have a benefit in the treatment of allergic rhinitis clinical improvement, reduction in severity of symptoms and decreased medication use in patients with seasonal allergic rhinitis and perennial rhinitis, although no effects were seen in the treatment of asthma [74]. It has been hypothesized that the addition of probiotics

to infant feeds may result in the reduction of sensitization to dietary allergens. A Cochrane review of 12 studies evaluating this premise concluded that there was insufficient evidence to recommend routine addition of probiotics to infant feeds although well designed studies are needed to conclusively address this issue [75].

Other Conditions

Studies have also reported possible benefits of probiotics in other areas including delaying *Pseudomonas* colonization and infection in critically ill patients [76], clearing of vancomycin-resistant enterococci colonization [77], treatment of mastitis during lactation [78], and prevention of recurrent urinary tract infection in women [79] and vulvovaginal candidiasis [80]. A Cochrane review suggested that there is a lack of sufficient evidence for or against recommending probiotics in the treatment of bacterial vaginosis and emphasized the need for well-designed randomized controlled trials. However, the authors noted a favorable outcome in the treatment of bacterial vaginosis with the use of metronidazole/probiotic and probiotic/estriol regimens [81]. The potential role of genetically engineered probiotics as vaginal microbicides to prevent HIV is provocative; however, it is in the early stages of development and further research in this field is needed [82].

SIDE EFFECTS

It has been well established that the intestinal microflora plays an important role in the metabolic activity and immune system of the host, and probiotics help to promote microflora. However, it can also be argued that manipulation of the normal microflora by probiotic use may theoretically increase the risk of adverse metabolic and immunomodulatory effects. Some minor adverse effects, including thirst and constipation with *S. boulardii* use [33], bloating and flatulence with *L. rhamnosus* GG use [83], nausea, vomiting, abdominal pain, rash, diarrhea and constipation, have been reported [84]. Although serious complications from probiotic use are exceedingly rare, given that probiotics are live microorganisms, it is conceivable that they may rarely result in invasive infections.

Mackay et al reported a case of *Lactobacillus* endocarditis with probiotic use in a patient with underlying mitral valve disease [85]. There was a case of liver abscess due to *Lactobacillus rhamnosus* reported in a diabetic patient who was consuming dairy products containing *L. rhamnosus* GG [86]. Kunz et al [87] and Land et al [88] reported cases of *Lactobacillus* sepsis associated with probiotic use in children. A case of recurrent *Bacillus subtilis* septicemia has also been reported in an immunocompromised patient [89] after the use of probiotics containing *B. subtilis*. There have also been several reported cases of *S. boulardii* fungemia associated with probiotic use. Most cases of invasive infections associated with probiotic use have occurred in patients with intravenous catheters [90–92], the elderly [93] and immunocompromised population [94,95].

These anecdotal case reports of infection after probiotic use have not been confirmed in larger studies. Salminen et al found no association of *Lactobacillus* bacteremia with the increase use of *L. rhamnosus* GG in a study conducted in Finland [96]. A small randomized controlled study involving 17 HIV patients also demonstrated no adverse events after a 2-week course of probiotic *L. rhamnosus* GG [97]. Similarly, the safety of the probiotics containing strains of *Lactobacillus* and *Bifidobacterium* was evaluated in infants and showed no adverse events [98–100].

CONCLUSION

There is a growing interest in probiotics and defining the proper use of these agents. Although probiotics seem to have beneficial effects in a large number of clinical conditions, the efficacy of probiotics is strain- and dose-dependent. Also, there are numerous clinical and methodological differences between trials (eg, strain used, dose, formulation), making it difficult to draw conclusions about efficacy. Thus far there is strong evidence to support their use in only a few conditions, including treatment of acute diarrheal diseases, prevention of antibiotic-associated diarrhea, and prevention of pouchitis. Additional research in the form of well designed, randomized, double-blind, placebo-controlled trials will be helpful in bolstering our evidence base. Although probiotics appear for the most part to be safe, caution should be used in specific subgroups of patients such as the immunocompromised, the elderly, and patients with indwelling intravenous catheters.

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